150/20 DR
AF 10/11/7/96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1003

Applicant: Paul R. Schimmel

Serial No: 08/249,689 Art Unit: 1805

Filed: May 26, 1994 Examiner: John Brusca

For: DESIGNING COMPOUNDS SPECIFICALLY INHIBITING RIBONUCLEIC ACID FUNCTION

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1 and 3-21 in the Office Action mailed April 17, 1996 in the above-identified patent application. A Notice of Appeal was mailed on August 19, 1996. A check in the amount of $150.00 for the filing of this Appellant's Brief is also enclosed.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the Massachusetts Institute of Technology.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal. There is a related application, Serial No. 07/929,834, in which a Notice of Appeal has been filed.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1 and 3-21 are pending. Claim 2 has been cancelled. Claims 1 and 3-21 are on appeal. The text of each claim on appeal is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

No amendments after final have been submitted.

(5) SUMMARY OF THE INVENTION

The present invention is a method for designing compounds which inhibit RNA function, and compounds which inhibit RNA function. The method involves determining the nucleotide sequence of a site in the RNA that is critical to function, determining the secondary and tertiary structure in the region of the critical site, determining the sequence and structure of nucleotides flanking the critical site, and synthesizing a compound that will

bind specifically to the critical site (page 5, lines 2-14, and page 6, lines 24-30). The claimed compounds can be made using the claimed method.

The specification provides extensive guidance for performing the steps of the claimed method. Specifically, procedures for determination of critical sequences in RNA are described at least on pages 9-18, with an overview of RNA mutagenesis analysis for determination of critical sites presented on page 9, methods of synthesizing mutant RNAs for analysis presented on pages 9-12, and specific examples of analysis of critical sites on tRNA presented on pages 12-18. Procedures for determination of the primary, secondary, and tertiary structure of RNA molecules were well known at the time of filing and are referred to on pages 7-8. Examples of molecules which interact with specific RNA sequence structures are provided on pages 18-22. Such examples provide guidance for the choice of structures which can interact with a critical site on an RNA molecule. Procedures for modeling such structures and their interactions with RNA are provided on pages 37-38. Procedures for synthesizing RNA-specific compounds are provided on pages 38-39.

(6) ISSUES ON APPEAL

The sole issue presented on appeal is that claims 1 and 3-21 are patentable under 35 U.S.C. § 112, first paragraph, since the specification, in combination with skill and knowledge in the art, enables those of skill in the art to make and use the claimed invention.

(7) GROUPING OF CLAIMS

Appellant submits that the claims stand or fall together.

(8) ARGUMENTS

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1 and 3-21 stand finally rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification fails to adequately teach those of skill in the art how to make and use the claimed invention. Appellant respectfully traverses this rejection.

In the Office Action mailed April 17, 1996, the Examiner stated that the rejection was maintained for the reasons set forth in the Office Action mailed August 29, 1995.

A careful review of the Office Action mailed August 29, 1995 indicates that the present rejection appears to be based on a holding that it would require undue experimentation to practice the claimed method. In that Office Action, the Examiner analyzes the claims and disclosure as suggested in *Ex parte Forman*, 230 USPQ 546 (Bd. App. 1986). In making this analysis, the Examiner makes numerous assertions and conclusions regarding the various factors to be considered and bases these assertions and conclusions on certain evidence or argument.

The standard for making a rejection based on 35 U.S.C. § 112, first paragraph is articulated in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (see also MPEP § 2164.01 and 2164.04). Initially, the Examiner must accept the objective truth of statements made in the

specification. If such statements are to be called into question, the Examiner is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements (*In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

Appellant submits that an analysis of whether undue experimentation is required to practice an invention involves a complicated weighing of several factors (*Ex parte Forman*). Appellant asserts that in analyzing these factors, the Examiner is initially burdened with establishing, through evidence or convincing argument, that it would require undue experimentation to practice the claimed invention. As indicated above, absent such evidence or reasoning, the objective truth of statements made in the specification are to be accepted.

In the Office Action mailed August 29, 1995, the Examiner noted that factors to be considered in determining whether undue experimentation is required include (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill level of those in the art; (g) the predictability of the art; and (h) the breadth of claims.

A. The Case for Undue Experimentation

After discussing these factors, the Examiner makes essentially the following analysis (page 6, Office Action mailed August 29, 1995):

(1) the skilled practitioner would initially look to the specification for guidance in practicing the invention;

(2) the specification does not provide sufficient guidance;

(3) the practitioner would then be required to look to the prior art;

(4) the prior art contains neither methods of producing inhibitory compounds that bind to the minor groove nor examples of such compounds;

(5) the practitioner would be forced to use empirical trial and error to produce inhibitory compounds that bind to the minor groove; and

(6) such trial and error experimentation represents undue experimentation.

Appellant initially notes that were it necessary to reach points (5) and (6), such experimentation might be undue (although this is not conceded). However, Appellant has provided a method which will prevent those of skill in the art from having to resort to such trial and error. Accordingly, the conclusion that undue experimentation would be required to practice the invention is based on conclusions (2) and (4) in the above-cited analysis.

B. The Amount of Guidance Presented

The Examiner states that conclusion (2) -- that the specification does not provide sufficient guidance -- is based on the discussion of enablement factors earlier in the rejection. In the discussion of enablement factors, the Examiner makes essentially the following analysis of the guidance provided in the specification:

(i) the amount of direction or guidance presented in the specification is limited to citations and discussions of prior art;

(ii) the application does not distinctly describe procedures to perform any of the steps of the method (in particular determination of secondary and tertiary structure and synthesis of a compound that will bind to a critical site in the RNA);

(iii) no guidance is given for the therapeutic use of a compound produced by the method of the invention;

(iv) eight working examples are presented in the specification;

(v) the working examples are "not drawn to the claimed method because the examples fail to demonstrate all steps of the method";

(vi) no example is given of the design or the existence of a compound that inhibits the function of an RNA molecule by binding to its minor groove; and

(vii) no example is given of a therapeutic use of a compound produced by the claimed method.

Appellant asserts that this analysis is insufficient to support conclusion (2) above because these statements are variously incorrect, irrelevant, of insufficient weight, and/or are not dispositive of the question at hand. Appellant initially asserts that statement (i) is incorrect since the specification contains more than just prior art references and discussion. In the Response mailed July 17, 1996, Appellant requested that the prior art nature of all guidance, as alleged, be specifically pointed out in the next communication from the Patent Office. In the Advisory Action mailed July 30, 1996, the Examiner indicated that it was not intended that discussion of prior art in the specification is improper or cannot be used to

enable a claimed invention, thus conceding that statement (i), as made, does not support the rejection. In support of Appellant's extensive citation of prior art in the specification, Appellant notes that each of the steps in the claimed method represents determinations which have been performed, in isolation or in partial combination, on numerous RNA molecules. The specification refers to many such examples and indicates that the procedures to be performed can be performed routinely by those of skill in the art. Appellant's invention lies in the recognition that (1) critical sequences in RNA molecules are useful sites for inhibiting function, and (2) these separate established procedures could be combined to provide a means of designing such inhibitory compounds. Thus, for the present invention -- which represents a new combination of procedures and which when performed together as claimed and for the claimed purpose results in a useful method -- it is entirely appropriate to provide the bulk of guidance for practice of the invention through reference to prior art procedures.

In regard to statement (ii) -- that the application does not distinctly describe procedures to perform any of the steps of the method -- Appellant asserts that the specification does describe the procedures for performing steps of the method. In fact, the specification provides extensive guidance for performing the steps of the claimed method. Specifically, procedures for determination of critical sequences in RNA are described at least on pages 9-18, with an overview of RNA mutagenesis analysis for determination of critical sites presented on page 9, methods of synthesizing mutant RNAs for analysis presented on pages 9-12, and specific examples of analysis of critical sites on tRNA presented on pages

12-18. Procedures for determination of the primary, secondary, and tertiary structure of RNA molecules were well known at the time of filing and are referred to on pages 7-8. Examples of molecules which interact with specific RNA sequence structures are provided on pages 18-22. Such examples provide guidance for the choice of structures which can interact with a critical site on an RNA molecule. Procedures for modeling such structures and their interactions with RNA are provided on pages 37-38. Procedures for synthesizing RNA-specific compounds are provided on pages 38-39. In view of this, it is not clear what the Examiner finds lacking. To the extent that statement (ii) is based on an implicit requirement that the specification present guidance in a particular form, Appellant disputes this for the reasons discussed above. To the extent that statement (ii) was intended to constitute evidence that the specification provides insufficient guidance, Appellant asserts that it fails to do so because the statement is conclusory without reference to support for the conclusion reached, and there is no argument presented establishing how the alleged lack of distinct description of method steps constitutes a lack of guidance in the context of the claimed invention.

In regard to statement (iii) -- that no guidance is given for the therapeutic use of a compound produced by the method of the invention -- Appellant submits guidance is provided for the therapeutic use of compounds produced by the claimed method (see, for example, pages 39-41). Notwithstanding this, Appellant notes that the claims *do not require any therapeutic effect* of such compounds. In this regard it is important to note that the claims are directed to compounds, or a method of making such compounds, *per se*. It is

axiomatic that only that which is actually claimed need be enabled.[1] Thus, for the specification to teach how to make and use the claimed invention, all that is required is sufficient disclosure to allow those of skill in the art to make compounds (using the claimed method) that bind to the minor groove and inhibit function of the targeted RNA in any setting. No therapeutic effect is required. In this regard, Appellant directs attention to *In re Gardner*, 475 F.2d 1389, 1392 (CCPA 1973), *reh'g denied*, 480 F.2d 879 (CCPA 1973), where the court emphasized that the subject matter within a broad claim need not be shown to have the same degree of utility; it is sufficient if the specification adequately discloses some use for all of the subject matter.[2]

Appellant submits that any indication that the compounds can be used *in vivo* is not germane to the question of whether use of a composition of matter (which can, in fact, be used other than *in vivo*) is enabled, since the claims are not limited to this use. The claims do not limit the use of the claimed compound in any way. Appellant agrees that the claimed

---

[1]see *Christianson v. Colt Industries Operating Corp.*, 822 F.2d 1544, 1565, 1 USPQ2d 1241, 1255 (Fed. Cir. 1987), *vacated, and remanded with instructions to transfer appeal to Court of Appeals for the Seventh Circuit*, 108 S. Ct. 2166, 7 USPQ2d 1109 (1988), *on remand*, 870 F.2d 1292, 1299, 10 USPQ2d 1352, 1357 (7th Cir. 1989) ("Because only the claimed invention receives patent law protection, the disclosures need generally be no greater than the claim.")("The 'invention' referred to in the enablement requirement of section 112 is the *claimed* invention").

[2]See also *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762 (Fed. Cir. 1984) ("the fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility."); *Ex parte Hozumi*, 3 USPQ2d 1059, 1060-61 (Bd. Pat. App. & Int'f 1987) (as to examiner's Section 112 rejection "based on an asserted lack of enablement with respect to the utilization of the entire genus disclosed in the antitumor utility disclosed": "it is not necessary that all of the compounds claimed be useful for every utility disclosed in an application"); *Ex parte Cole*, 223 USPQ 94, 95 (PTO Bd. App. 1983) ("We know of no statutory or case law requiring each and every compound within a claim to be equally useful for each and every contemplated application.").

compounds *can* be used *in vivo*, but submit that they can also be used in other settings, such as *in vitro*. For example, on page 4, lines 10-16, and on page 5, lines 26-29, the specification indicates use of the claimed compounds for inhibition of bacteria and viruses, without limiting such inhibition to *in vivo* settings. In this regard, Appellant notes that such inhibition can be useful in, for example, cell culture. As discussed above, Appellant is only required to enable a single use for the claimed composition. Appellant asserts that all of the claimed compounds can be used at least *in vitro* and so the specification does teach how to use each of the claimed compounds.

Furthermore, Appellant asserts that even for the therapeutic uses at issue, Appellant is not required to support or demonstrate some arbitrary level of use or effectiveness. All that is required is that the invention work to some extent and that this minimal level of use is enabled. For example, it is not required that the claimed compounds cure any disease, prolong life, or even inhibit the function of a target RNA for some specific period of time. All that is required is that the claimed compounds, at a minimum, bind to the minor groove and inhibit the function of a single RNA molecule in any setting. Appellant asserts that the claimed compounds will accomplish this. Again, Appellant asserts that all of the claimed compounds can be used at least *in vitro* and so the specification does teach how to use each of the claimed compounds. Contrary to the assertion of the rejection, the "use" of the claimed compounds enabled by the specification need not be a commercially viable

therapeutic or even a therapeutically efficacious treatment.[3] Appellant is not required to demonstrate a safe and effective therapeutic, especially when the claims do not require such a capability. Accordingly, statement (iii) is both incorrect and not germane to the question of enablement of the claimed invention.

In regard to statement (iv) -- that eight working examples are presented in the specification -- Appellant agrees that the specification has eight numbered working examples. However, the specification also describes numerous other examples of individual steps in the claimed method, and examples of specific interactions of molecules with RNA molecules. In this regard, Appellant again emphasizes that the claimed method is a combination of procedures known in the art and for which examples of application of such procedures are known and described in the specification.

In regard to statement (v) -- that the working examples are "not drawn to the claimed method because the examples fail to demonstrate all steps of the method" -- Appellant notes that the rejection fails to establish how the absence of a single complete working example, using all of the steps of the claimed method, prejudices enablement. In this regard, Appellant notes that there is no requirement that the claimed method be actually

---

[3]see *In re Langer*, 183 USPQ 288, 298 (CCPA 1974) (full scale clinical trials in humans...may be necessary to establish 'commercial usefulness' in this technology. However, development of a product to the extent that it is commercially salable in the marketplace is not required to establish 'usefulness'); see also *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'f 1987) (appeal presents "only one issue...whether [applicants] have provided substantiating evidence...to establish that the subject matter defined [in the claims] possesses a practical utility"; "the issue under 35 USC 112 relating to an enabling disclosure is subsumed within the issue under 35 USC 101 relating to patentable utility"); *In re Hafner*, 410 F.2d 1403, 1405, 161 USPQ 783, 785 (CCPA 1969) ("The disclosure of how to use must relate to a use of the kind considered by the Supreme Court in Brenner v. Manson to be a sufficient utility.").

demonstrated.[4] Appellant asserts that the rejection implies that the lack of such a "complete" example weighs against enablement. As discussed above, however, due to the nature of the claimed invention (i.e. the new combination of known and established procedures), Appellant submits that examples drawn to individual steps represent, collectively, exemplification of the claimed invention. No reasoning has been provided as to why it matters that the claimed method is exemplified in a composite manner.

In the Advisory Action mailed July 30, 1996, the Examiner notes that the specification fails to describe or cite prior art describing design of compounds that bind to the minor groove of RNA, and that the record does not indicate that this aspect of the invention has been reduced to practice. Appellant again notes that the is no requirement that the invention be actually demonstrated or actually reduced to practice. Although Appellant is aware that whether or not the invention has been actually demonstrated is a *factor* to be considered in determining whether an invention is enabled, it is not alone dispositive of enablement, nor is it the cornerstone of any *rule* of enablement. Appellant believes that this factor has been applied as indicating lack of enablement *per se*. The evidence of this is that no analysis has been presented setting forth *why* a lack of demonstration of this step of the invention leads to a *conclusion* of lack of enablement. The fact that the Examiner *feels* that the invention is not enabled is not sufficient.

---

[4]See *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987) (the mere fact that something has not previously been done is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it).

In regard to statement (vi) -- that no example is given of the design or the existence of a compound that inhibits the function of an RNA molecule by binding to its minor groove -- Appellant notes that extensive guidance is provided for the design of inhibitory compounds (see, for example, pages 37-38, and the discussion of known examples of compounds which interact with RNA on page 18-22). Appellant respectfully points out that, to the extent that molecules are known which bind to specific critical sites in RNA molecules (such as portions of proteins responsible for specific RNA binding), examples of the required compounds exist which can be adapted for the design of new compounds according to the claimed method.

In regard to statement (vii) -- that no example is given of a therapeutic use of a compound produced by the claimed method -- Appellant again notes that the claims do not require any therapeutic effect and so the presence or absence of examples of such a therapeutic effect is not germane to the question of enablement.

In view of the incomplete, incorrect, and undeveloped nature of the "evidence" of lack of guidance presented in the rejection, as discussed above, and the fact that extensive guidance for the procedures necessary to practice the claimed invention appears in the specification, Appellant asserts that this factor weighs heavily in favor of enablement.

C. The State of the Prior Art

In the Office Action mailed August 29, 1996 the Examiner states that conclusion (4) -- that the prior art does not provide methods for producing inhibitory compounds -- is based

on the discussion of the prior art earlier in the rejection. In the discussion of the prior art, the Examiner makes essentially the following analysis:

(i) relatively little progress has been made towards generating compounds that specifically interact with critical sites on RNA molecules;

(ii) a survey of the prior art does not reveal examples of drugs that inhibit RNA molecules by binding to the minor groove;

(iii) some publications cited in the specification involving compounds which bind to nucleic acids or nucleotides do not indicate that the molecules bind to the minor groove of RNA or to nucleic acids;

(iv) Wilson *et al.*, *Biochemistry* 32:4098-4104 (1993), published three years after the priority date, was cited as indicating that no classes of small molecules binding to the minor groove of RNA have been defined by that time.

In regard to points (i), (ii), and (iv), Appellant notes that those of skill in the art were, and are, unaware of Appellant's invention, and it is not clear what efforts had been made to obtain compounds specifically binding to the minor groove of RNA. Appellant notes that the prior art was clearly able to design and study compounds that interact with the nitrogenous base portion of nucleotides (see discussion below). Wilson *et al.* describe *initial* efforts, apparently started years after the present invention was made, to identify compounds that interact specifically with RNA. In addition, Wilson *et al.* describes not efforts to *design* such compounds, but a screening of compounds known to interact with **DNA**. Wilson *et al.*

does not describe any attempts, nor is there any suggestion, to screen compounds either at random or based on any criteria other than known binding to DNA. Wilson *et al.* also does not describe attempts by others to either design or screen compounds which bind to RNA. Thus, it is clear that although Wilson *et al.* falls within the generic concept of attempts to *discover* RNA binding compounds, Wilson *et al.* does not involve any attempt to *design* such compounds. Accordingly, Wilson *et al.* does not characterize any attempts to *design* RNA binding compounds. With respect, this fact goes to the weight of any alleged absence of RNA binding compounds. Specifically, it is much less prejudicial to enablement if few if any attempts had been made to practice this aspect of the claimed method (as appears to be the case), than if numerous attempts at such *design* had ended in failure (for which there is no evidence on the record). In this regard, Appellant notes that the record indicates that Wilson *et al.* was cited as alleged evidence that molecules binding the minor groove of RNA had not been designed even three years after the priority date of the present application. While such an indication, if present in Wilson *et al.*, would be a factor to be used in determining enablement, it is at best a secondary factor. Such an indication, even if clearly made by Wilson *et al.*, would hardly justify the sweeping *conclusion* now attributed to Wilson *et al.* by the Examiner.

Similarly, the probative value of the comment by Wilson *et al.* that there are no outstanding paradigms to suggest design directions for RNA groove-binding drugs is in serious doubt because the present application, unknown to Wilson *et al.*, describes such a

paradigm. Furthermore, this belief expressed in Wilson *et al.* that no such paradigm exists indicates that Wilson *et al.* was unaware of any systematic effort to *design* compounds that interact with RNA molecules based on any paradigm such as the one conceived by Appellant. Thus, the alleged failure to produce such compounds contained in Wilson *et al.* carries little weight regarding any alleged difficultly in practice of the present invention. Appellant asserts that the Examiner has failed to rebut this analysis of Wilson *et al.*

In the Advisory Action mailed July 30, 1996, the Examiner states that Wilson *et al.* was "cited to show that three years after the priority date of the instant application, one of ordinary skill in the art would not know how to practice the claimed invention in the absence of additional guidance from the instant application." The Examiner goes on to note that Appellant has failed to point to any prior art that contests the teachings of Wilson *et al.* Appellant does not doubt that Wilson *et al.* was cited for the reason stated by the Examiner. However, Wilson *et al.* does not, in fact, support the Examiner's statement. Initially, Appellant notes that Wilson *et al.* does not indicate in any way that "one of ordinary skill in the art would not know how to practice the claimed invention in the absence of additional guidance from the instant application", nor has the Examiner previously contended that it did. It appears that the Examiner intended to allege that Wilson *et al.* provides evidence that one of ordinary skill in the art would not know how to practice the claimed invention in the absence of additional guidance from the specification. Wilson *et al.* does not, in fact, show this since Wilson *et al.* is unaware of the specification!

In regard to point (iii) -- that some publications cited in the specification involving compounds which bind to nucleic acids or nucleotides do not indicate that the molecules bind to the minor groove of RNA or to nucleic acids -- the Examiner criticized publications cited in the specification -- Yamada *et al.*, *Nucleic Acids Research* 8:5767-5777 (1980), and Wank *et al.*, *J. Mol. Biol.* 236:1001-1010 (1994) -- as failing to show that tuberactinomycin binds to the minor groove of RNA. The Examiner also criticized Rebek *et al.*, *J. Am. Chem. Soc.* 109:5033-5035 (1987), Jeong and Rebek, *J. Am. Chem. Soc.* 110:3327-3328 (1988), and Askew *et al.*, *J. Am. Chem. Soc.* 111:1082-1090 (1989), as discussing interaction of synthetic molecules with purines and pyrimidines rather than nucleic acids. Appellant initially notes that at least Askew *et al.* does discuss interaction with nucleic acids (see Scheme II, page 1087). Another publication cited in the specification (and of record), Rebek, *Science* 235:1478-1484 (1987), discusses compounds which can be used to bind to the major and minor grooves of nucleic acids (see paragraph bridging pages 1482 and 1483). Appellant submits that these publications clearly indicate that compounds were known having specific interactions with nucleic acids, and that the structural basis for these interactions were known in detail. The authors of each of these publications were clearly conversant with the principles of the design of compounds having specific molecular interactions. Appellant asserts that this state of the art (and this level of skill and knowledge in the art) clearly supports enablement of the present claims. The concepts, techniques, and knowledge necessary to produce specifically interacting compounds were known. What is lacking in the

prior art is the proper combination of techniques, and the direction in which to apply them, which is provided by Appellant's invention as described in the specification. Accordingly, Appellant asserts that the state of the prior art was sophisticated enough to allow design of compounds which bind to critical sites in RNA without the need for undue experimentation. In this regard, Appellant notes that no reasoning has been presented as to why or how undue experimentation would be required in view of the state of the prior art.

D. Other Factors

As for the other factors to be considered in determining whether undue experimentation is required, although these were discussed by the Examiner, it is not clear how or if they were considered in arriving at the conclusion that undue experimentation would be required since they are not referred to in the analysis on page 6 of the Office Action mailed August 29, 1995. It is noted that the Examiner admits that some factors favor enablement. For example, the Examiner notes that the level of skill in the art is high and admits that the structure and location of critical sites of a number of RNA molecules have been successfully characterized in the prior art. The Examiner also mischaracterizes several of the other factors. For example, the Examiner states that the nature of the invention is the design of compounds with therapeutic utility which inhibit the function of an RNA molecule by binding to the minor groove. In fact, the claims do not require that the compounds have a therapeutic utility. The Examiner asserts that it is not predictable which nucleotides are critical for function in an RNA molecule. While this may be true *a priori*, the invention

requires, and the specification describes, predictable procedures for determining the location of critical sites. That is, the procedure for determining which sites are critical can be performed as described in the specification with predictable results (i.e. the location of critical sites will be determined). The Examiner also fails to characterize the amount of experimentation required. Accordingly, the other factors to be considered do not clearly support a conclusion that undue experimentation would be required to practice the claimed invention.

It appears from the lack of support for most bases offered for the present rejection (see discussion above), and the rebuttal offered in the Office Action mailed April 17, 1996, that the crux of the present rejection is the question of whether or not it would require undue experimentation to actually design a compound that would bind to a critical site within the minor groove of an RNA molecule, thereby inhibiting the RNA function for which the site is critical. In support of the conclusion that undue experimentation would be required for those of skill in the art to effect such a design, the Examiner notes that no such compounds are presented and that such compounds were not being commercially produced three years after the priority date of the present application. Appellant agrees that these factors are relevant to the determination of whether undue experimentation would be required. However, Appellant submits that more than this is required to establish that undue experimentation would be required and thereby support a *prima facie* case of lack of enablement. The Examiner bears more of a burden than just listing such factors. In this regard, Appellant notes that

arguments in the Office Action mailed April 17, 1996 clearly imply that, in making the present rejection, the Examiner improperly considers it to be Appellant's burden to provide evidence in the prior art or specification that the claimed method can be practiced. In fact, the objective truth of statements in the specification that such compounds can be designed is to be believed unless evidence or convincing reasons to doubt them are presented. In the present case, all that has been presented is a lack of evidence that compounds binding to the narrow groove of RNA have been commercially produced. No evidence and no convincing argument has been presented that such design could not be accomplished. Without this, Appellant submits, no *prima facie* case of lack of enablement has been established.

Notwithstanding the above argument, Appellant has previously submitted a Declaration of Dr. Paul R. Schimmel Under 37 C.F.R. §1.132 (mailed July 28, 1992) in which Dr. Schimmel, an expert in the art of the analysis of RNA structure and rational design of compounds, and an expert in the knowledge of those of skill in this art, indicates that those of skill in the art at the time the invention was made could routinely design compounds binding to RNA given knowledge of the structure of the site of binding. Accordingly, absent evidence or convincing argument to the contrary, this aspect of the claimed method could be practiced without the need for undue experimentation.

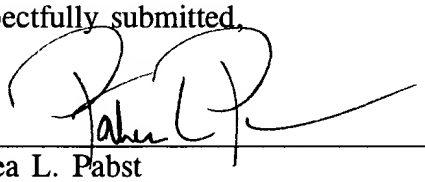
Appellant respectfully submits that, for all of the foregoing reasons, the claims on appeal meet the standards of 35 U.S.C. § 112, first paragraph.

(9) SUMMARY AND CONCLUSION

Appellant asserts that claims 1 and 3-21 are patentable under 35 U.S.C. § 112, first paragraph, since the specification, in combination with skill and knowledge in the art, enables those of skill in the art to make and use the claimed invention. Appellant has shown that the Examiner has failed to establish a proper *prima facie* case of lack of enablement. Appellant has also shown that, even had such a case been established, the record as a whole indicates that the claimed invention is enabled by the specification.

For the foregoing reasons, Appellant submits that the claims 1 and 3-21 are patentable.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: October 17, 1996

ARNALL GOLDEN & GREGORY
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8794
(404) 873-8795 (fax)

Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Teresa Spratt

Date: October 17, 1996

APPENDIX

Claims on appeal:

1. A method for designing a compound specifically inhibiting targeted ribonucleic acid function comprising the steps of:

(a) determining the nucleotide sequence in the targeted ribonucleic acid that is critical to function;

(b) determining the secondary structure of the region of the targeted ribonucleic acid in which the critical site is located;

(c) determining the three-dimensional structure of the targeted RNA, including the position of the critical site relative to the major and minor grooves;

(d) determining the sequence of nucleotides and structure flanking the critical site in the targeted ribonucleic acid that is specific to the critical region of the ribonucleic acid to be inhibited and within the minor groove; and

(e) synthesizing a compound that will bind specifically to the critical site within the minor groove of the targeted ribonucleic acid thereby inhibiting targeted ribonucleic acid function.

3. The method of claim 1 wherein the ribonucleic acid is selected from the group consisting of mRNA, rRNA, tRNA and viral RNA.

4. The method of claim 1 wherein inhibition of targeted ribonucleic acid function inhibits protein synthesis.

5. The method of claim 4 wherein protein synthesis is inhibited in cells selected from the group consisting of tumor cells, virally infected cells, and bacterial cells.

6. The method of claim 1 wherein the three-dimensional structure is modeled using sequences of the RNA and calculating the minimum energies for these structures.

7. The method of claim 1 wherein the critical region of the targeted ribonucleic acid is determined by mutation of regions of the targeted RNA and comparison of the function of the mutated RNA with the original RNA, wherein mutations that result in mutant RNA having altered function indicate that the site of mutation is a critical site.

8. The method of claim 1 wherein the targeted RNA is a tRNA, wherein the critical region of the tRNA is determined by site directed mutation of the tRNA and analysis of the function of the mutated tRNA.

9. The method of claim 1 further comprising determining an effective amount of the compound and combining the compound with a pharmaceutical carrier.

10. The method of claim 9 wherein the carrier is selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

11. A compound specifically binding to and inhibiting the function of a targeted RNA molecule, wherein the compound is specifically directed to and binds to a critical region of the RNA molecule, located within the minor groove of the RNA molecule, identified by a combination of the primary, secondary and tertiary structure of the critical region.

12. The compound of claim 11 wherein the RNA is selected from the group consisting of mRNA, tRNA, rRNA, and viral RNA.

13. The compound of claim 11 further comprising a pharmaceutically acceptable carrier selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

14. The method of claim 3 wherein the critical site is in the minor groove of the acceptor stem of a tRNA molecule.

15. The method of claim 14 wherein the tRNA molecule is $tRNA^{Ala}$.

16. The method of claim 15 wherein the critical site is the G3:U70 base pair.

17. The compound of claim 12 wherein the compound binds to a critical region within the minor groove of the acceptor stem of a tRNA molecule.

18. The compound of claim 17 wherein the tRNA molecule is $tRNA^{Ala}$.

19. The compound of claim 17 wherein the critical region is the G3:U70 base pair.

20. The method of claim 1 wherein the compound is a nucleic acid and the compound is synthesized *in vivo* from a retroviral vector.

21. The compound of claim 11 wherein the compound is a nucleic acid and the compound is synthesized *in vivo* from a retroviral vector.

TABLE OF CONTENTS

(1) REAL PARTY IN INTEREST

(2) RELATED APPEALS AND INTERFERENCES

(3) STATUS OF CLAIMS ON APPEAL

(4) STATUS OF AMENDMENTS

(5) SUMMARY OF THE INVENTION

(6) ISSUES ON APPEAL

(7) GROUPING OF CLAIMS

(8) ARGUMENTS

(9) SUMMARY AND CONCLUSION

Certificate of Mailing

Appendix: Claims on Appeal

Table of Contents